Supplementary Online Content

Halperin F, Ding S-A, Simonson DC, et al. Roux-en-Y gastric bypass surgery or lifestyle with intensive medical management in patients with type 2 diabetes: feasibility and 1-year results of a randomized clinical trial. *JAMA Surg*. Published online June 4, 2014. doi:10.1001/jamasurg.2014.514.

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Exclusion criteria, description of Why WAIT program, medication adjustment algorithm, and recruitment

Additional Information on Exclusion Criteria:

Uncontrolled T2D was defined as consistent fasting blood glucose >200 mg/dl or HbA_{1c} above twice normal. Gastrointestinal disease exclusions included previous major gastrointestinal surgery, inflammatory bowel disease, esophageal diseases including severe intractable esophagitis, Barrett's Disease, esophageal dysmotility or other impaired gastric motility (gastroparesis), or hiatal hernia >3 cm in size, chronic or acute bleeding conditions including peptic ulcer disease, portal hypertension (gastric or esophageal varices), chronic pancreatitis, or cirrhosis of the liver; malignancy (including personal or family history of Medullary Thyroid Carcinoma (MTC) or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)), except participants who have been disease-free for greater than 5 years, or whose only malignancy has been basal or squamous cell skin carcinoma, or debilitating medical conditions, severe cardiopulmonary disease including uncontrolled hypertension (repeated systolic measures >160 or diastolic > 95 mm Hg on more than one day), unstable angina pectoris; recent myocardial infarction, history of coronary artery bypass surgery or angioplasty within 6 months; congestive heart failure, arrhythmia, stroke or transient ischemic attacks, sustained urinary albumin excretion >1000 mcg/mg cr, or serum creatinine ≥1.5mg/dL with creatinine clearance <60 ml/min by Cockcroft-Gault equation and eGFR <60 ml/1.73 m2/min, by Modification of Diet in Renal Disease (MDRD) study equation, any endocrine disorder other than T2D or thyroid disease which is stable on replacement therapy, including Cushing's syndrome; any history of eating disorder unless it was in stable remission for over 3 years although binge eating symptoms were not exclusionary, history of drug and/or alcohol abuse within 2 years of the screening visit, history of impaired mental status by DSM4 (Diagnostic and Statistical Manual, 4th Edition) criteria and including, but not limited to active substance abuse, a history of schizophrenia, borderline personality disorder, uncontrolled depression, suicidal attempts within the past two years or current suicidal tendencies or ideations. Subjects were excluded for significant weight loss (>3%) within the previous 3 months, or participation in alternate medically supervised exercise or weight reduction program within the previous 3 months, or use of prescription or over the counter weight reduction medications or supplements within one month of the Screening Visit and for the duration of study participation. Subjects needed to be non-smoking for ≥ 2 months. Women who were lactating, planning pregnancy, or unwilling to use contraception during the course of the trial were excluded.

Description of Weight Achievement and Intensive Treatment (*Why WAIT*) program:

Weight Achievement and Intensive Treatment (Why WAIT) is a 12-week multidisciplinary program for weight control and intensive diabetes management designed by Joslin Diabetes Center for application in a multidisciplinary diabetes practice environment [1]. The 12-week initiation phase included diet, exercise, behavioral and educational support followed by monthly one-on-one support sessions for a total of one year (maintenance phase). Participants were enrolled in small cohorts of 10-15 participants to encourage group interaction, cohesion, and support. Key aspects of the Why WAIT program include: 1) Intensive and interactive medication adjustments, 2) Structured modified dietary intervention, 3) Graded, balanced, and individualized exercise intervention, 4) Cognitive behavioral intervention and 5) Group education.

Participants attended the clinic one evening for 2 hours each week. At the beginning of each group intervention session, participants were weighed by the study Registered Dietician (RD). Participants' blood glucose meters were downloaded. The Why WAIT certified diabetes nurse educator (CDNE) reviewed the blood glucose data and adjusted diabetes medications accordingly. Participants then attended a 60-minute exercise session supervised by the Why WAIT Registered Clinical Exercise Physiologist (RCEP). Following the exercise session, participants gathered in a relaxed atmosphere, suitable for adult learning and interaction, for the behavioral or didactic sessions.

Though adapted from the two previous models used in the DPP [2] and the Look AHEAD [3] studies, this evidence-based model is distinctly different in the following points:

1) *Intensive and interactive medication adjustments*. Whenever applicable, diabetes medications are changed or adjusted by an endocrinologist using an algorithm in order to reduce or eliminate anti-hyperglycemic medications that may contribute to weight gain while increasing or initiating others that have neutral or positive impact on body weight [4]. Medications are adjusted weekly based on daily intensive blood glucose monitoring including before and after exercise.

2) *Structured modified dietary intervention*. Universally, men are recommended to start an 1800 calorie diet and women on a 1500 calorie diet that advanced by 300 calorie reduction if 3% weight loss is not achieved by the sixth week. Nutrient recommendations include approximately 40-45% of calories from carbohydrate, less than 35% from fat with saturated fat below 7%, and 1-1.5 gram per kilogram of adjusted body weight protein (or around 20-30% from protein) and 15 grams of fiber per 1000 calories, according to the Joslin nutrition guidelines for overweight and obese patients with diabetes [5]. All participants are instructed to use diabetes specific meal replacements for both breakfast and lunch and encouraged to eat two snacks between meals [6,7]. For dinner, participants are instructed to select from 14 different structured menus that were designed from the food that most Americans eat to improve dietary adherence but modified to follow the same macronutrient composition. At the sixth week, participants are provided with alternative menus for breakfast and lunch equivalent in caloric content and composition to the meal replacement and offered to either continue to use the meal replacement, the natural food for breakfast and lunch, or to alternate between them.

3) *Graded, balanced and individualized exercise intervention*. An individualized exercise plan is designed to have an intensity level that was set above the minimum required to improve the participant's current exercise capacity, but below a level that may evoke abnormal clinical signs or symptoms. It includes a balanced mix of aerobic exercise (cross and interval training), resistance exercise (circuit and superset training) and flexibility exercise (stretching). The exercise plan includes a weekly 60-minute exercise session under supervision of an exercise physiologist. The aim of the graded exercise program is to gradually advance to 300 minutes per week [8] with emphasis on resistance exercise to maintain the lean body mass (*supplemental* ***eTable 1***).

4) Cognitive behavioral intervention. Group behavioral support sessions are conducted weekly during the initial 12 weeks of intervention followed by individual coaching once monthly during the follow-up period. Each behavioral session is led by a clinical psychologist or social worker. Sessions incorporate key validated components of cognitive-behavioral therapy for diabetes management and weight loss (*supplemental* ***eTable 2***).

5) *Group education.* Group didactic sessions are conducted over the initial 3 months. Each 30-minute session discusses different topics relevant to weight management and/or diabetes control. Participants are provided with handouts for future reference. Educational sessions are conducted by the program's diabetologist, exercise physiologist, registered dietician or psychologist.

6) *Service coding and reimbursement.* The Why WAIT program was designed to offer multidisciplinary complementary services with appropriate reimbursement in compliance with insurance regulations. All services are recognized as reimbursable but levels of payment are different based on the third-party payer requirements for authorizations and co-payments. The Why WAIT model of intervention was successfully implemented in diabetes practice at the Joslin Diabetes Center in Boston, MA since 2005.

Algorithm for Medication Adjustments:

The following guidelines were used to standardize the medical management of T2D in both the surgical and medical treatment arms of the study. The general guidelines were adhered to as much as possible; however, all treatment decisions were made on an individual basis by patient providers depending on the clinical scenario, which may have required digression from the algorithm. All prescription medications were prescribed only as approved by the FDA, with no off-label drug use. Thus, there were differences between the treatment algorithms for the medical and surgical study arms resulting from preferential use of antidiabetic medications with weight loss or weight neutral effects compared to those associated with weight gain. Many such agents were not utilized in the post-operative setting, such as incretin modulators, and/or pramlintide. Within this constraint, we established as much concordance as possible in the management of T2D between the medical and surgical study groups.

1) *Medical Management of T2D in the surgical study arm*: During peri-operative bariatric surgery hospitalization average blood glucose goals were below <180 mg/dl. Insulin was used for hyperglycemia inpatient management. After surgery, insulin and oral diabetes therapies were stopped (if appropriate).

After hospital discharge, subjects were advised to monitor blood glucose one to four times daily depending on glycemic control. If the fasting glucose was above 200 mg/dl on two consecutive days, metformin was (re)started. If the fasting glucose remained above 200 mg/dl one week later, metformin dose was increased or sulfonylureas were added or resumed. If one week later the fasting glucose still remained above 200 mg/dl, the sulfonylurea dose was increased or insulin was added or resumed initially in the form of long-acting basal insulin, and then short-acting prandial as needed. Incretin modulators (GLP-1 receptor agonists or DPP4 inhibitors) and pramlintide were not prescribed to post-bariatric surgery study participants.

For the first nine months post-operatively from bariatric surgery, during which period rapid ongoing weight loss would be expected to improve glycemia, pharmacologic therapy was added for HbA_{1c} equal or above 8%, or estimated average glucose (eAG) equal or above 180 mg/dl, in the following order: metformin, sulfonlyurea, then insulin. If the HbA_{1c} fell below 8%, insulin or oral medications were dose reduced or stopped. After the ninth month post-operatively from bariatric surgery, if the HbA_{1c} remained equal or above 7% or the eAG equal or above 126 mg/dl, then medications were added in the order previously described (metformin, then sulfonylurea, then insulin or thiazolidinedione). If at any time the HbA_{1c} fell to 6.5% or below (eAG below 140 mg/dl), and/or the average fasting blood glucose equal or below 100 mg/dl, then diabetes medications, including metformin, were discontinued.

2) *Medical Management of T2D in the WhyWait Program:* During the first 12 weeks of the program when participants were seen weekly, the first step was to add metformin, or continue it for those already on it, and increase it to maximum dose (2500 mg QD) as tolerated. GLP-1 receptor agonists were added, if tolerated. If GLP-1 receptor agonists were contraindicated or not tolerated, then a DPP4 inhibitor was used instead. If patients were on insulin, thiazolidinedione, or sulfonylurea at program start, these were stopped or the dose reduced in the order above, if glycemia goals permitted. If hyperglycemia persisted on metformin, incretin modulator, sulfonylurea, then basal insulin was added before prandial insulin, unless specific meal coverage was necessary.

During the entire follow-up period lifestyle modification was reinforced at each encounter. If the HbA_{1c} was not at goal metformin was added or increased, as applicable. If still not at glycemic goal, medications were added in the following order as needed: GLP-1 receptor agonist or DPP4 inhibitor, sulfonylurea, long-acting basal insulin and then short acting prandial insulin with or without pramlintide. If participants reached HbA1c below 6.5% or eAG below 140 mg/dl, medications were stopped or reduced in the following order: thiazolidinedione (if used), sulfonylurea, DPP4 inhibitor, metformin, and finally GLP-1 receptor agonist.

Recruitment:

Community outreach for potential participants included recruitment materials in primary care and specialty clinics, internet postings institutional clinical research websites, as well as Craig's list, ClinicalTrials.gov and Center Watch, along with press releases and advertisement in local papers. In addition electronic medical record search engines identified potentially eligible patients for care providers to use to send Institutional Review Board approved recruitment study materials. Reasons for not pursuing the study for those potential participants initially contacting the study team, but not coming to a clinical trial orientation session are provided in ***eTable 4***. ***eTable 5*** provides reasons provided by potential participants coming to a clinical orientation session for not pursuing screening and additional trial involvement.

eTable 1. Progression of Exercise Intervention in Why WAIT Program

Week	Exercise Duration Goal	Exercise Procedure
Week 1 – 4	20-30 minutes 3 to 4 days per week	Aerobic and flexibility exercises performed at the Joslin gymnasium, starting with low-resistance high repetitions. Duration and frequency of exercise will increase gradually.
Week 5 – 8	45 minutes 5 days per week	Circuit training will be added to the supervised exercise in addition to 20-25 minutes of aerobic exercise, including 7 exercise stations for upper and lower body muscle groups, with exercise for 50 seconds at each station and move to the next station in 10 seconds. The 7-station circuit will be repeated twice, under instruction and supervision by the RCEP.
Week 9 – 12	45-60 minutes 6 days per week	Participants will start a fitness challenge. Fitness challenge champion will be announced on week 12. Participants will continue to engage in resistance and circuit training up to 4 days per week, as well as aerobic and flexibility exercises up to 6 days per week.

eTable 2: Group Didactic Core Curriculum in Why WAIT Program

Week	Presenter/Duration	Title and Content
Week 1	All team members (60 min)	Introduction to the team and participants. Dietician will present details on the recommended meal plan. Exercise physiologist will present details on the recommended exercise plan. The study psychologist will review ground rules for group participation. Individual questions will be answered by the team.
Week 2	Registered Dietician (30 min) Psychologist (30 min)	Balancing the calorie scale Realistic goal setting and learning from your logbook
Week 3	Exercise Physiologist (30 min) Psychologist (30 min)	Take action – be active Changing problem eating patterns for good
Week 4	Psychologist (60 min)	When thoughts get in your way
Week 5	Physician (60 min)	For your health, not your shape: what science says?
Week 6	Registered Dietician (30 min) Psychologist (30 min)	Making sense of portion distortion Managing cravings through mindful eating
Week 7	Exercise Physiologist (30 min) Psychologist (30 min)	Burn the fat through strength training Stress management
Week 8	Psychologist (60 min)	Relapse prevention
Week 9	Exercise Physiologist (30 min) Psychologist (30 min)	Stay active – keep it off Maintaining weight loss success
Week 10	Physician (60 min)	Science, Lifestyle and Food
Week 11	Registered Dietician (30 min) Psychologist (30 min)	Keeping out of the fast-food lane Successful social eating
Week 12	All team members (60 min)	Changing for life – putting it all together

eTable 3: Sensitivity Analysis for Primary Outcome Measures Including All Randomized Participants

Endpoints:	12 months (number (%)) RYGB (n = 22)	12 months (number (%)) Why WAIT (n = 21)	*P*-value [a]
Primary Endpoint			
HbA_{1c}<6.5% and FBS<126 mg/dl	11 (50%)	3 (14%)	0.017
Meeting ADA Treatment Goals			
HbA_{1c} <7.0%	15 (68%)	4 (19%)	0.008
LDL-C <100 mg/dl	15 (68%)	9 (43%)	0.064
Systolic BP <130 mm Hg	16 (73%)	11 (52%)	0.147
Meeting all three goals	11 (50%)	1 (5%)	0.007
Normoglycemia			
HbA_{1c} <6.0%	6 (27%)	0 (0%)	0.042 [b]
FPG <100 mg/dl	14 (64%)	3 (14%)	0.002
Meeting both criteria	6 (27%)	0 (0%)	0.025 [c]

Endpoints:	Baseline mean (SD)		10% Weight Lost or 3 months Baseline adjusted mean change (95% Confidence Interval)		12 months Baseline adjusted mean change (95% Confidence Interval)		*P*-value [d]
	RYGB	Why WAIT	RYGB	Why WAIT	RYGB	Why WAIT	
BP, mm HG							
Systolic	130.9 (12.7)	125.6 (14.1)	-6.6 (-12.5 to -0.7)	-5.6 (-11.4 to 0.2)	-11.6 (-18.0 to -5.2)	0.6 (-5.7 to 6.9)	0.007 [e]
Diastolic	81.6 (7.8)	76.4 (8.3)	0.9 (-2.3 to 4.1)	-4.2 (-7.4 to -1.0)	-5.1 (-8.3 to -1.8)	-2.4 (-5.8 to 1.0)	0.003 [e]
Cholesterol, mg/dL							
Total Cholesterol	156.5 (34.7)	166.3 (39.9)	-19.1 (-32.9 to -5.3)	-4.2 (-17.9 to 9.5)	-3.7 (-18.2 to 10.8)	7.7 (-7.5 to 23.0)	0.109
Triglycerides	133.5 (90.0)	150.4 (75.1)	-34.5 (-45.9 to -23.1)	-33.3 (-44.5 to -22.0)	-49.3 (-65.9 to -32.6)	-7.8 (-25.1 to 9.4)	0.016 [f]
HDL-C	43.5 (9.5)	40.4 (10.2)	-6.0 (-8.7 to -3.4)	-0.1 (-2.8 to 2.6)	10.0 (6.5 to 13.4)	0.1 (-3.5 to 3.8)	0.001 [e]
LDL-C	88.7 (27.0)	101.7 (30.2)	-7.6 (-19.1 to 4.0)	-4.5 (-16.2 to 7.1)	-5.6 (-17.9 to 6.8)	8.5 (-4.6 to 21.5)	0.222

Abbreviations: ADA, American Diabetes Association; BP, blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density cholesterol; LDL-C, low-density cholesterol; RYGB, Roux-en-Y gastric bypass; Why WAIT, Weight Achievement and Intensive Treatment

[a] P values are logistic regression between group corrected for baseline, unless noted.
[b] P value is exact logistic regression corrected for baseline.
[c] P value cannot be adjusted for both baseline HbA1c and fasting glucose due to no patients with HbA1c<6.0% in the Why WAIT program, thus this reported P-value is unadjusted for baseline.
[d] P values represent treatment effects from linear mixed model corrected for baseline, unless otherwise noted.
[e] P-value represents time x treatment interaction; treatment effect not significant.
[f] P value for time x treatment interaction also significant at P <0.05.

HDL = high density lipoprotein
LDL = low density lipoprotein, directly measured

eTable 4: Reasons for Phone Inquiry Failures Provided in Order of Frequency

Reason	Number of participants	(%)
Total Phone Inquiry Failures	**674**	**100**
BMI >42 kg/m^2	111	16.5
Unwilling to have surgery	105	15.6
Lost to follow up	93	13.8
Hemoglobin A_{1c} < 6.5 % and/or no diabetes medications; and/or duration of diabetes <1 year	76	11.3
Geography not permitting adherence to visit schedule	62	9.2
Medical History meets other exclusion criteria*	58	8.6
Age >65 years	51	7.6
BMI <30 kg/m^2	29	4.3
No Formal Diagnosis of Type 2 DM	28	4.2
Previous Why Wait participant	20	3.0
Previous bariatric surgery	14	2.1
Type 1 DM	9	1.3
Other: Participating in another study (4), Did not want to be randomized (4), Language barrier (3), Time constraints (2), No medical insurance (2), Not interested in participating with no additional information (2), Inadequate compensation (1)	18	2.7

*Exclusion criteria other than age, BMI or diabetes specific

eTable 5: Reasons for Not Pursuing Screening Visit and Additional Trial Involvement Following Attendance in Clinical Trial Orientation Session

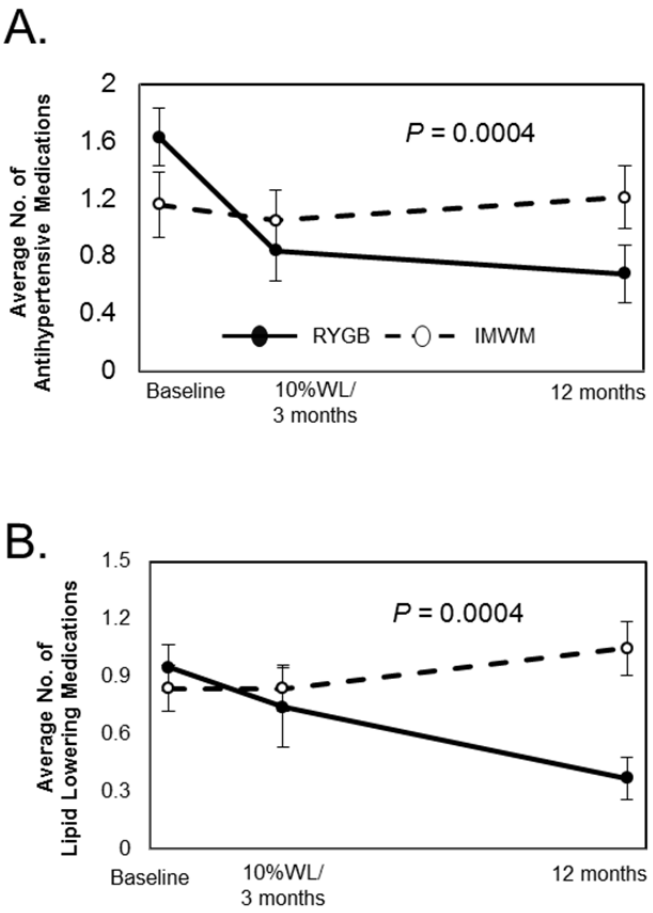
Reason	Number of participants	(%)
Total participants	**55**	**100**
Unable to contact	35	63.6
Unwilling to have surgery	10	18.2
Decided to pursue surgery outside trial	6	10.9
Too much individual data collection required	2	3.6
No insurance	1	1.8
Unwilling to participate in Why WAIT	1	1.8

eTable 6: Baseline Characteristics of Patient-Reported Outcomes by Study Group.

Baseline scores:	Roux-en-Y Gastric Bypass	Intensive Diabetes and Weight Medical Management (Why WAIT)
SF-36 (total)	66.24 (17.75)	71.56 (12.38)
SF-36 (physical health)	61.32 (19.66)	68.61 (13.22)
SF-36 (mental health)	63.49 (16.24)	63.67 (11.88)
PAID	52.63 (16.38)	56.18 (12.59)
Barriers to being active	2.84 (2.36)	2.37 (1.71)
EQ-5D index	0.80 (0.15)	0.87 (0.09)
EQ-5D visual analog scale	65.11 (17.67)	64.19 (14.16)
IWQOL	81.5 (26.42)	68.63 (17.50)

[a] Data expressed as mean (SD)

eFigure. Average of the number of blood pressure–lowering medications [**A**] and lipid-lowering medications [**B**] is shown by treatment group and time. P-value represents treatment effect from linear mixed model, variance shown is standard error. [●] RYGB; [○] IMWM.



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